CHAPTER 126
PAEDIATRIC TRANSPLANTATION

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Introduction

Paediatric transplantation is still considered a difficult task in the African continent. Lack of resources, cadaveric programs, and technical facilities, as well as delayed referral of cases are among the important obstacles that need to be overcome in order to start transplantation programs. South Africa has a well-established cadaveric program for kidneys and liver, and success related to both is found in Egypt and some North African countries. The progress of immune suppression, intensive care, and nutritional support will lead to improvement in more African countries in the near future.

Liver Transplantation

Liver transplantation is now the standard treatment for end-stage liver disease (ESLD) in children. Children had paved the way for transplantation since the beginning of the procedure; the initial cases were performed by Thomas E. Starzl on two children in 1963 and 1968. Now, more than 500 paediatric patients recieve transplants every year; this number of transplant procedures has been relatively stable since the mid-1990s, but there has been a shift to utilisation of an increasing number of "partial" liver grafts from cadaveric and living donors. Due to organ scarcity and size problems, paediatric liver transplantation is considered a challenge. Donors younger than the age of 5 years comprise only 26% of the paediatric cadaveric donors. As a consequence, split-liver, living-related, and—much less now—reduced liver techniques are important in paediatric transplantation. Survival has been significantly improved and now approaches 90% at 1 year and 80% at 5 years. Many children survive into adolescence and adulthood with good quality of life (QOL) as a consequence of technical improvements, intensive care unit (ICU) advances, early transplantation, and the huge changes in immune suppression.

Indications

The most common indications of childhood transplantation are currently classified into groups:

- ESLD due to cholestatic and noncholestatic causes of cirrhosis;

- acute hepatic failure;

- stable liver disease with remarkable morbidity and/or a known mortality;

- some metabolic liver diseases;

- select tumours; and

- a variety of miscellaneous indications.

One of the major indications in children is liver disease that limits long-term survival or quality of life or markedly impairs normal growth and development. Cirrhosis alone is not an indication for transplantation because many of these patients can be medically managed for a prolonged period before decompensation. In acute liver failure, the development of clear symptoms such as refractory coagulopathy, acidosis, and cerebral oedema that correlate with a poor prognosis for spontaneous recovery of liver function is an indication for transplantation. Otherwise, medical support in those patients with a better prognosis is provided until liver function returns to normal.

Children usually present with decompensation of hepatocellular function or portal hypertension, including progressive jaundice, coagulopathy, protein-calorie malnutrition and growth retardation, impaired cognitive development, encephalopathy, hypersplenism, variceal haemorrhage, and advanced or refractory ascites. The majority of patients undergoing transplantation in this population are deeply jaundiced due to secondary or primary biliary cirrhosis from long-standing intrahepatic and/or extrahepatic biliary obstruction. On physical examination, these patients often have muscle wasting; an enlarged spleen; a hard, palpable liver; abdominal distention from ascites; and peripheral oedema. With decompensation, long-term survival without liver transplantation is limited; referral for transplantation must be made before decompensation.

Neonatal Cholestatic Liver Diseases

Cholestatic liver disorders—the most common being biliary atresia—are the most common indications for transplantation in children. Biliary atresia accounts for 70% of this cholestatic group, which itself represents 60% of all transplanted children per year. The management of biliary atresia rests on early diagnosis and portoenterostomy if diagnosis precedes the development of cirrhosis, usually before 3 months of age. Although long-term results from portoenterostorny are optimal if it is peformed before 8 weeks of age, only 20–25% of all atresia patients will not need transplantation. In many cases, however, portoenterostomy allows reasonable growth and development so that transplantation is forestalled until the child is older and larger. Liver transplantation is indicated when the diagnosis is made in infants older than 3 months of age, when ESLD is clearly present at any age, or after a portoenterostomy failure. Jaundice and malnutrition are the problems with most of these children, who present in very bad condition (especially in the African continent). Preparation for transplantation is therefore extremely difficult and many children could die while awaiting the procedure.

Other uncommon causes of cholestatic liver injury and cirrhosis include familial paucity of intrahepatic bile ducts, which exists in syndromic (e.g., Alagille syndrome) and nonsyndromic forms; familial cholestatic syndromes (progressive familial intrahepatic cholestasis); primary or secondary sclerosing cholangitis; and uncorrectable choledochal cyst disease, including Caroli's disease. All of these conditions proceed to jaundice, cirrhosis, and portal hypertension.

Noncholestatic cirrhosis

Causes of cirrhosis and ESLD include autoimmune hepatitis, neonatal hepatitis, chronic viral (B or C) hepatitis, and cryptogenic cirrhosis.

Fulminant hepatic failure

Fulminant hepatic failure is encephalopathy within 28 days after the onset of jaundice in a patient with acute liver failure without evidence of chronic liver disease. Acute liver failure of an undefined type makes up the largest group within fulminant hepatic failure, followed by drug toxicity, toxin exposure, and previously unrecognised metabolic

disease. Acute liver failure includes profound coagulopathy, acidosis, hypoglycaemia, and progressive hyperbilirubinaemia. These patients can develop acute renal failure, multiorgan failure syndrome, or cerebral oedema progressing to herniation. Deterioration in coagulation is one of the major parameters to indicate transplantation in these conditions. Transplantation should be done before the patient develops coma stage IV, when the prognosis is extremely dire.

Metabolic liver disease

Metabolic liver disease disorders have in common an enzyme deficiency or some other defect in hepatocellular function. This impairment can result in progressive fibrosis or cirrhosis (e.g., cystic fibrosis, chronic Wilson's disease, and neonatal iron storage disease) with a typical presentation of ESLD. In other cases, the liver is structurally normal but harmful by-products of metabolism accumulate to cause neurologic injury (e.g., Crigler-Najjar syndrome, ornithine transcarbamylase deficiency, and Wilson's` disease); cardiovascular disease (e.g., familial hypercholesterolaemia); or renal injury (familial hyperoxaluriain, in which case both kidney and liver should both be transplanted). Some disorders are associated with the development of malignancies, such as tyrosinaemia, and transplantation should be considered preemptively.

Tumours

Hepatoblastoma is now considered a good indication for transplantation in cases of an unresectable tumour with no extrahepatic spread and initial good response to chemotherapy. Living-related transplantation with removal of the vena cava has been reported with good results in few sporadic cases. Hepatocellular carcinoma is primarily seen in older children with viral hepatitis or in association with cirrhosis from other causes. Nonmetastatic malignancies in paediatric patients are managed by surgical resection unless tumour size and/or location preclude resection. The long-term survival after liver transplantation for hepatoblastoma is approximately 60%, whereas outcomes from hepatocellular carcinoma are not nearly as good. The major issue that remains to be resolved is whether transplantation should be attempted for large hepatoblastomas primarily or as salvage after recurrence postresection. Data from Europe suggest a worse outcome when liver transplantation is performed as a salvage procedure. The most common benign tumour of the liver is haemangioendothelioma; and although the vast majority regresses with growth and medical therapy, occasionally heart failure or mass effect warrants transplantation.

Miscellaneous

Other conditions that may indicate transplantation include diagnoses such as Budd-Chiari syndrome, trauma, and biliary cirrhosis secondary to intestinal failure and long-term use of total parenteral nutrition.

Contraindications to Transplantation

Contraindications to transplantation include HIV-positive serology patients, extrahepatic malignancy, metastatic liver malignancy, terminal nonhepatic pathology, uncontrolled systemic sepsis, and irreversible neurological damage.

Pretransplant Care

Many problems present in cases with evidence of ESLD who are candidates for liver transplantation. Most cases are below the fifth percentile with regard to weight and height, and those with ascites, malnutrition, bad coagulation profile, and haematemesis are very difficult to handle. Vaccination is another issue that should be dealt with before transplantation because living attenuated vaccine cannot be used posttransplantation due to immune suppression. Therefore, most presenting children receive nutritional support, oral decontamination, and a full battery of investigations. Radiology is used to assess the patency of vessels (the portal vein in cases of biliary atresia), the presence of port-caval shunts, and the vascular anatomy of the recipient. Another problem is timing— at the time a paediatric donor is available, a size-matched paediatric recipient may not be available. This, of course, is not the case in living-related liver transplantation (LRLT), when scheduled transplantation is the case and the problem of being put on a waiting list is removed.

In 2002, the Pediatric End-stage Liver Disease (PELD) score was implemented to allocate organs based on the "sickest first" paradigm. The PELD score consists of five variables:

1. International Normalised Ratio;

2. total serum bilirubin concentration;

3. serum albumin level;

4. growth retardation (= 2 standard deviations below the median height or weight for age); and

5. young age (much less than 1 year, or 1 to 2 years of age).

Status I is used to designate patients with fulminant hepatic failure, primary graft nonfunction after transplantation, early hepatic artery thrombosis, and miscellaneous acute conditions. Unlike the case for adults, paediatric ESLD patients requiring care in an ICU for any reason are listed as status I because their mortality is high despite a minimal change in PELD score. In an effort to ameliorate the shortage of potential organs, the livers of all donors 18 years of age and younger are preferentially allocated to paediatric recipients. This protocol, combined with the widespread use of split-liver transplantation, has markedly reduced waiting times and positively impacted waiting list mortality.

The Surgical Procedure

The donor hepatectomy

The use of organs from cadaveric donors in paediatric liver transplantation involves selecting an appropriate quality- and size-matched donor, organising an experienced transplant harvest team, and performing a precise technical operation that recognises arterial anatomic variants and allows for multiorgan procurement. The advent of segmental liver transplantation has expanded the acceptable donor age to approximately 40 years. Preharvest donor management should focus on maintenance of haemodynamic stability with adequate but not excessive volume loading, minimising the use of vasopressors, optimising oxygenation without excessive use of positive end expiratory pressure (PEEP), and correcting hypernatraemia that results from diabetes insipidus. In the stable donor, once these goals are achieved, the procurement operation can be performed. In the properly selected unstable donor, unnecessary delays are to be avoided because expedient hypothermic perfusion and cold storage only help to minimise the ongoing organ ischaemia.

1. The donor operation begins with midline laparotomy and median sternotomy for wide exposure.

2. The abdominal great vessels are exposed by a medial visceral rotation of the right colon and small intestine, and the aorta and inferior mesenteric vein are cannulated.

3. The liver quality is assessed, and the biliary tree is flushed via the gallbladder.

4. After full systemic heparinisation, the supraceliac aorta is cross-clamped and the intrapericardial inferior vena cava is incised to exsanguinate the donor.

5. Cold-organ perfusion is then initiated through the previously placed cannulas, and the abdominal cavity is immersed in ice in an attempt to achieve a liver core temperature of 4°C.

The University of Wisconsin (UW) solution has been used as the standard preservation solution in the United States since 1987, when it was developed by Belzer and Southhard. This solution extends the limit of preservation to as long as 12–18 hours, after which the incidence of primary graft failure increases substantially. However, the acceptable preservation time depends on numerous donor and recipient variables and should still be minimised when possible. This is especially important in instances of reduced size or split-liver transplantation. The UW solution is a hyperkalemic, hyperosmolar solution that

prevents cellular swelling, maintains stable transmembrane electrical gradients upon reperfusion by preventing efflux of intracellular potassium during storage, and contains a variety of oxygen-free radical scavengers. Recently, some centres have employed a histidine-tryptophan-ketoglutarate solution because of its low potassium content and viscosity. Once the donor organ is procured, the harvest team typically transports the liver graft to the transplant centre and prepares it for engraftment by a separate recipient team.

Segmental liver transplantation

Segmental liver transplantation can be of three kinds: living-donor, reduced-size, and split-liver.

Living-related transplantation

In living-related transplantation, the donor is investigated preoperatively with extensive radiologic evaluation regarding vascular anatomy as well as biliary and volumetry of the liver lobes. The choice of the graft depends on the expected volume in relation to recipient weight. Segments 2 and 3 (left lateral segment, or LLS) are usually suitable for children who weigh less than 25 kg. Older children can have segments 2, 3, and 4, or even the right lobe in adolescents. The ratio between liver weight and recipient weight should be above 1% to avoid a small-for-size graft. Grafts of more than 5% of body weight, however, have a bad prognosis due to the large size of the graft in relation to the child's abdomen and the compartmental syndrome that might occur.

Reduced-size transplantation

Due to the small but real risk of safety in a healthy donor, reduced-size transplantation was simultaneously developed as an alternative method. It involves resecting the LLS graft before or after cold-organ perfusion and discarding the remaining liver. Obviously, this benefits the paediatric recipient but wastes an organ that could be used by an adult recipient.

Split-liver transplantation

Splitting the whole organ into a right trisegrnent and an LLS graft to utilise in an adult and paediatric recipient, respectively, was first described by Pichlmayr in Hanover, Germany, in 1988. This can be done either before cold-organ perfusion (in situ technique) or after cold-organ perfusion and removal of the liver from the donor (ex vivo technique). This technique provides a suitable graft for the paediatric population without worsening the already severe organ shortage in the adult population.

The recipient operation

The procedure for total hepatectomy is the same for living-related and cadaveric transplantation, except for vena cava removal, which is not done in living-related or split-liver procedures.

This procedure for total hepatectomy has changed little over the past two decades. Whereas there are tremendous individual and institutional differences in the subtleties of using certain techniques, the basic steps in the procedure remain the same. The procedure can roughly be divided into four major phases, each with its own anatomic and physiologic challenges: hepatectomy phase, anhepatic phase with engraftment, reperfusion with arterialisation, and biliary reconstruction.

Perhaps the most challenging step during liver transplantation is the hepatectomy. Coagulopathy, portal hypertension, and poor liver and renal function create a surgical environment in which continuous bleeding is possible. During this phase, the anaesthesiologist plays a key role in maintaining volume and rapid transfusion, correcting coagulopathy and fibrinolysis, and maintaining body temperature. The goal of this phase is to devascularise the liver by ligating and dividing the hepatic artery and portal vein as well as mobilising the suprahepatic and infrahepatic vena cava to enable removal. At the authors' institution, the strategy is to leave at least one hepatic artery perfusing the liver until the graft is ready, and to ligate it just before removing the liver. This procedure has been found to reduce the lactacidosis during the anhepatic phase. These goals are achieved while leaving in the recipient adequate lengths of each vessel for later implantation of the donor graft. In the majority of paediatric liver transplant operations,

the rettohepatic vena cava is retained as the liver is dissected off the vena cava by dividing the tributaries from the right and caudate lobes; often, only partial occlusion of the vena cava is necessary. Meticulous but expedient surgical technique is essential during the hepatectomy in ensuring optimal patient outcome. During the anhepatic phase, the anaesthesiologist must support certain aspects of hepatic function to prevent or treat acidaemia, hypothermia, coagulopathy, and occasionally fibrinolysis. In addition, the anaesthesiologist must ensure adequate circulating volume and maintain haemodynamic stability. Veno-venous bypass is rarely used in children.

1. While the patient is anhepatic, the liver graft is removed from hypothermic storage and engrafted. The insertion of the graft begins with the suprahepatic vena caval followed by the infrahepatic vena caval in cases of cadaveric full liver.

2. If the retrohepatic cava was retained, the "piggyback" technique is used, in which the hepatic vein of the graft is sewn to the cloacae created from the confluence of the recipient hepatic veins.

3. Next is portal vein anastomosis with careful suturing to avoid twisting, adding a growth factor to the sutures to avoid stenosis.

4. Before reperfusion the liver is flushed with a cold colloid or albumin solution via the donor portal vein to reduce the risk of potential reperfusion-associated complications.

5. Reperfusion is undertaken in a controlled manner by first removing the suprahepatic vena cava clamp, then the infrahepatic vena cava clamp, and lastly the portal venous clamp; or, in case of LRLT, the hepatic venous then portal anastomoses, respectively.

Communication between the surgical and anaesthesia teams at the time of reperfusion is essential to allow the anaesthesiologist time to institute preparative and preventive measures.

As blood is reintroduced into the liver allograft and allowed to drain into the right atria, many serious and potentially life-threatening complications can develop. The major challenges encountered by the anaesthesiologist at this point are life-threatening hyperkalaemia, acidosis, arrhythmias, and haemodynamic instability with or without surgical or coagulopathic bleeding. A contributing factor is the return of cold, acidotic, and hyperkalemic blood directly into the right atrium. It is at this point that maintenance of physiologic stability by the surgeon and anaesthesiologist in the preceding phases, the preoperative state of the recipient, and the intrinsic quality of the graft converge to determine early graft function as well as the course of the remainder of the operation. Without a doubt, this is one of the most hazardous portions of the liver transplant procedure.

1. The hepatic arterial anastomosis is then performed. In some cases, when the arteries are small calibre (<3 mm), the arterial anastomosis is performed before reperfusion. In general, though, arterial inflow is obtained from one of the branches of the celiac trunk. In some instances, however, inflow from these vessels is not adequate, necessitating the use of aortic conduits. A conduit can be placed either on the supraceliac or infrarenal aorta.

2. The biliary tree is then reconstructed by choledochocholedochostomy or by Roux-en-Y choledochojejunostomy, the latter being more common in biliary atresia cases, in small children, and used exclusively in partial liver grafts because of the size of the donor duct.

3. After ensuring sufficient haemostasis, drains are placed, and the abdominal cavity is closed. In cases of large-for-size grafts, those with a graft weight-to-recipient's body weight ratio (GRWR) >4–5, the abdomen is closed over a synthetic prosthesis only so as not to kink the vessels and compromise the graft; this prosthesis can be removed a few days later.

4. The patient is then transferred directly to the ICU.

Postoperative Care

Very close follow up is the mainstay of posttransplant care in children. Most of the patients will have a very short period of ventilation unless there is pulmonary hypertension, and some of the patients are extubated in the theatre. Regular laboratory investigations to detect early manifestations of sepsis, rejection, or vascular insult are mandatory, even in asymptomatic patients. Duplex study is done daily in the first 2 weeks to detect vascular flow, changes in wave patterns, areas of congestion, and biliary radicles.

Graft function can be assessed in many ways. Physiologic and clinical assessment can be done almost immediately. A warm, arousable, and haemodynamically stable patient with a graft producing "golden-brown" bile is the hallmark of a functional graft. Failure of a graft without vascular compromise (primary nonfunction) requires retransplantation in almost all cases, with the outcome directly related to the time to retransplantation. The incidence of primary nonfunction in paediatric patients is 5–10%. Renal functions should be assessed accurately, and the possibility of systemic hypertension and diabetes due to immune suppression is assessed.

Technical Complications

Technical complications can be divided into vascular, biliary, and general surgical complications. In the early postoperative period, infectious and general surgical complications of liver transplantation today are similar to those that occur after any major abdominal operation. However, the incidence of fungal infection is higher and the incidence of bowel perforation in paediatric recipients is as high as 19% in some series.

Vascular complications

Major vascular complications include hepatic artery thrombosis, portal vein thrombosis, and vena caval thrombosis or stenosis. Intravenous low-dose unfractionated heparin is used for prophylaxis to prevent vascular thromboses in some centres. In the authors' unit, aspirin is the only drug used for its antiplatelet effect. Early detection is essential. For rapid management, duplex ultrasonography (US) is usually the first line for diagnosis because it is done routinely. Computed tomography (CT) or conventional angiography are accepted means of diagnosis.

Hepatic artery thrombosis (HAT) is the most common vascular complication, with an incidence that varies from 5% to 18%, depending on patient age and type of graft. Early vascular complications are usually technical in nature, whereas immunologic and infectious (e.g., cytomegalovirus, or CMV) causes have been ascribed to those occurring months after transplantation. HAT occurring in the first week after liver transplantation is commonly associated with graft nonfunction and biliary necrosis or leak. Those instances occurring later do not necessarily affect graft function immediately but can produce biliary complications, including intrahepatic biliary abscesses, biliary anastomotic stricture, and sclerosing cholangitis with sepsis, all of which lead to significant morbidity.

If diagnosed early, some patients can be managed by thrombectomy and surgical revision. However, most patients with early HAT require urgent retransplantation. Late HAT with preserved graft function can be managed by radiologic interventional techniques, and the patient can undergo retransplantation remote from the time of the initial transplant procedure. Thrombosis of the portal vein occurs in 2–4% of paediatric liver transplant procedures and is usually associated with loss of the graft. Prompt retransplantation is required for patient salvage. Late portal vein thrombosis usually presents as recurrent variceal bleeding or ascites and can be managed medically, endoscopically, or surgically with either shunting or retransplantation. Vena caval or hepatic vein thrombosis or stenosis occurs in 3–6% of paediatric liver transplant patients and is manifested with ascites or pleural effusion; it is usually best managed with balloon dilatation in an interventional radiology unit.

Biliary complications

Biliary complications that are not associated with HAT occur in 3–20% of patients, depending on the type of graft and whether a choledochojejunostomy was employed. These complications usually result from technical errors, but occasionally warm ischaemia or immunologic and infectious factors can be implicated (e.g., CMV). Diagnosis is achieved by cholangiography, and treatment can be by endoscopic or radiologic intervention or by surgical revision.

Immunosuppressive therapy and rejection

Immunosuppression for liver transplantation in the modern era rests on a class of drugs known as calcineurin inhibitors (CNI), the prototype of which is cyclosporine. Cyclosporine—especially its microemulsion formulation, which allows better bioavailability and more consistent therapeutic levels—revolutionised organ transplantation by reducing the incidence of rejection in all solid organs. The second-generation CNI tacrolimus was first used clinically in 1990. The greater potency of tacrolimus allowed for a further reduction in the early incidence of rejection after liver transplantation while also allowing earlier weaning of corticosteroid therapy. Initial reports of a higher incidence of opportunistic infections and posttransplant lymphoproliferative disorders have been refuted by modem data. Currently, most liver transplantation centres utilise a tacrolimus-based regimen combined with corticosteroid therapy with or without adjunctive agents such as mycophenolate mofetil (MMF).

Cyclosporine and tacrolimus share certain acute and long-term side effects while having some that are unique to each agent. The most important of these is nephrotoxicity, which occurs in an acute variety from vasoconstriction of the afferent renal arterioles and is reversible, as well as a more chronic variety marked by tubular atrophy, interstitial fibrosis, and glomerulosclerosis. The chronic variety is variably reversible, depending on the degree of disease. To minimise acute toxicity and to allow lower early CNI levels, especially with pretransplant renal insufficiency, a purine antimetabolite mycophenolate mofetil is sometimes used as an adjunctive agent.

The newest class of immunosuppressive agents are the inhibitors of the mammalian target of rapamycin, the prototype of which is sirolimus. This agent has been used sparingly in paediatric liver transplantation, and only preliminary data regarding its efficacy are available. Although this drug has no nephrotoxicity, it is associated with other long-term sequelae, such as hypercholesterolaemia. At present, there are no perfect immunosuppressive agents available.

Acute rejection is common in paediatric liver transplantation, with the peak incidence occurring within the first 6 months; 30–50% of patients experience at least one episode. Acute rejection is less common after the first posttransplantation year, occurring in less than 10% of cases. Diagnosis of acute rejection is suspected when elevated aspartate or alanine transaminase levels or elevated alkaline phosphatase levels and gamma-glutamyl transferase levels are observed. Acute rejection is an alloantigen specific, T-cell-mediated inflammatory process that targets vascular endothelium and biliary epithelium but not hepatocytes. This is related to the greater expression of donor human leukocyte antigens on the former cell types. The histologic hallmark of acute rejection is a mixed inflammatory cell infiltrate (polymorphonuclear cells, lymphocytes, and eosinophils) in the portal triad with evidence of endotheliitis and/or biliary epithelial injury. Rejection is graded as mild, moderate, or severe, depending on the proportion of involved portal triads, the degree of infiltrate and injury, and the presence of central vein endotheliitis, which is a sign of severe acute rejection.

Treatment of acute rejection is centred on a high-dose methylprednisolone bolus, but unresponsive cases may require use of antibody therapy (OKT-3, ATG). Acute rejection does not influence long-term graft survival in adults or children unless it occurs in multiple or corticosteroid refractory episodes. Acute rejection accounts

for less than 3% of overall patient and graft loss. However, treatment of acute rejection is an important risk factor for the development of cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections in children. The latter is then a risk factor for the development of posttransplant lymphoproliferative disorder. Therefore, a balance between adequate immunosuppression to prevent acute rejection and over-immunosuppression to avoid toxicity is necessary. Currently, long-term morbidity from immunosuppressive drug therapy is the major challenge facing long-term survival and QOL in the paediatric solid organ transplantation population.

Chronic rejection is a common cause of late graft loss in children; disease recurrence is uncommon. Chronic rejection is not entirely alloantigen driven and may be due to a number of factors that share a final common pathway of graft injury. The hallmark of chronic rejection is the intrahepatic loss of bile ducts, which has been termed "vanishing bile duct syndrome" owing to this histological finding noted on biopsy. Rejection is suspected by the presence of progressive jaundice and a rising serum alkaline phosphatase level. Currently, there is no prophylactic or therapeutic agent available to treat chronic rejection, although progression of graft fibrosis may be forestalled by sirolimus, based on animal data. The only accepted treatment when decompensated graft failure occurs is retransplantation.

Infectious complications

Posttransplant infections are the most common cause of morbidity and mortality after liver transplantation. The highest incidence of bacterial and fungal infections occurs in the first month after transplantation.

Table 126.1: Agents responsible for infectious morbidity, their presentation, diagnosis, and treatment.

Organism	Presentation	Methods of diagnosis	Antimicrobials
Cytomegalovirus (CMV)	Infection results from: reactivation of virus; blood transfusion; infected transplanted organ. Mild viral, "flu-like" syndrome Invasive tissue infection (retinitis,pneumonitis, myocarditis, enterocolitis, hepatitis, central nervous system)	Quantitative CMV-DNA PCR PP-65 antigen Tissue cultures Blood or fluid cultures Biopsy with immunostains	Prophylaxis: intravenous ganciclovir, oral valganciclovir Therapy: intravenous ganciclovir with or without CMV immunoglobulin
Epstein-Barr virus (EBV)	Spectrum: infectious mononucleosis to lymphoproliferative disease to lymphoma to EBV-associated soft tissue tumours Occurs with EBV and immunosuppression, 10% to 15% infant liver transplantation Gastrointestinal tract, neck, thorax, central nervous system	Quantitative EBV-DNA PCR Blood smear Biopsy with immunostains CT scans of suspected sites	Prophylaxis: intravenous ganciclovir, oral valganciclovir Therapy: acyclovir, reduction or withdrawal of immunosuppression. Possible use of systemic chemotherapy for lymphoproliferative disorders or lymphoma
Herpes simplex virus (HSV)	Skin lesions, gastrointestinal tract disseminated herpes: fever, fatigue, abnormal liver functions, hepatitis, pneumonia	HSV-1 and HSV-2 antibodies Biopsy with viral cultures	Acyclovir
Pneumocystis	Atypical pneumonia, can progress to life-threatening pneumonitis	Bronchoalveolar lavage, lung biopsy	Prophylaxis: Low-dose oral trimethoprim/ sulfamethoxazole, dapsone, or pentamidine Therapy: High-dose intravenous trimethoprim/ sulfamethoxazole
Candida	Local mucous membrane, invasive tissue infection, fungemia	Blood, fluid, and tissue cultures, fundoscopic examination	Prophylaxis: Fluconazole, in very-high-risk patients possibly lipid formulation of amphotericin B Therapy: Fluconazole (for sensitive candidal species) or lipid formulation of amphotericin B, caspofungin, or voriconazole (insensitive Candida or Aspergillus)
Aspergillus	Entry via upper or lower respiratory tract with metastatic spread (central nervous system, intraabdominal, solid organ)	Blood, fluid, and tissue cultures, Bronchoalveolar lavage, CT scans	
Bacteria	Gram-negative: Enterobacteriaceae, Escherichia coli, Pseudomonas Gram-positive: Enterococcus, Staphylococcus	Blood, fluid, and tissue cultures Bronchoalveolar lavage, CT scans, surgical exploration	Varies

Fungal infections occurring months to years after transplantation are unusual and are more commonly the atypical or endemic organisms, such as *Cryptococcus, Mucor, Blastomyces,* or *Coccidioides* species. Viral infections are the most common infections after the early posttransplant period. CMV and EBV infections account for the vast majority of opportunistic viral infections. Overall reduction and more selective immunosuppression and prophylaxis with ganciclovir have reduced the incidence and morbidity of these infections. The other agents responsible for infectious morbidity, their presentation, diagnosis, and treatment are included in Table 126.1.

Of particular importance in children is the prophylaxis and effective treatment of EBV. This is associated with the development of numerous malignant consequences, the most common of which is a diffuse proliferation of lymphoid tissue known as posttransplant lymphoproliferative disorder. This disorder can present as a mononucleosis-like syndrome with diffuse lymphadenopathy or as lymphoma involving any organ. A variety of other tumours are also associated with EBV infections. The general therapy for posttransplant Iymphoproliferative disorder is reduction or elimination of immunosuppression and, occasionally, surgical intervention and/or chemotherapy. The complete discussion of these disorders is beyond the scope of this chapter.

Outcome

Numerous factors are known to impact patient and graft survival in children after liver transplantation. Overall, survival has improved, with 1-year and 5-year patient survival approaching 90% and 80%, respectively, in patients younger than 18 years of age. Age, nutritional status, urgency of transplantation, the indication for transplantation, and presence of renal dysfunction are all major factors that determine outcome. Whereas early data have suggested that patients with biliary atresia have worse outcomes due to their often malnourished state, young age, and previous surgical intervention, more recent data suggest that this difference is not significant. Patients with metabolic disease do exceedingly well because they often are older, do not have liver failure and its sequelae, and have not previously undergone an abdominal operation. Finally, transplantation for malignancy in children is associated with survival that is substantially below average but much better than the natural history of the disease. Numerous large series exist in the literature detailing the improvement in outcome with experience.

Although outcomes have improved, many issues remain to be resolved. The first and foremost is organ shortage. The number of listed patients awaiting liver transplantation is increasing steadily, whereas the number of suitable donors, even with segmental liver transplantation, has plateaued. Strategies aimed at expanding the donor pool and allocating organs to those patients who have not only the greatest survival benefit compared with pretransplant survival but also the greatest chance of optimal posttransplant outcome are essential. National policies aimed at effectively identifying donors amenable for organ splitting and development of local, regional, and national sharing of split grafts still await refinement.

Finally, the development of gene therapy or optimisation of hepatocyte transplantation as alternatives to whole organ transplantation for metabolic diseases may alleviate some of the current organ shortage.

Another important challenge for the liver transplantation community is the perfection of immunosuppression. Currently, all immunosuppressive agents have long-term side effects that result in impaired growth and development, infectious morbidity, malignancies, and numerous medical complications, including renal failure. The development of drug therapy that minimises or eliminates these complications is essential. Furthermore, a better understanding of the immunology of peripheral T-cell tolerance and chronic rejection is important. Although the past decade has witnessed improvements in many technical and immunosuppressive aspects of liver transplantation, improvements in survival and QOL in the next decade will rest firmly on a better understanding of the human immune system on cellular and molecular levels. The quest to achieve immunotolerance has been elusive.

Intestinal Transplantation

Patients with intestinal failure (IF) will not be able to maintain a normal state of nutrition, fluid and electrolyte balance, nor normal growth and development. Because total parenteral nutrition (TPN) is only a supportive modality that does not restore normal intestinal function, it is not a cure for IF. Besides, TPN is an expensive modality and has many serious long-term complications.

The prognosis for patients who develop severe complications from parenteral nutrition is poor. In this category of patients, it should be stressed that intestinal transplantation (ITx) is the only life-saving treatment with an unequivocal and well-proven survival advantage. The problem, however, is that all too often, transplant surgeons are confronted with patients being referred to ITx too late and in extremely bad general condition.

Historical Aspect

The experimental era of ITx was initiated by Lellehei and associates in 1959, and the transplantation of a multivisceral composite graft was performed by Thomas E. Starzl in 1960. The 1960s and 1970s saw nine published attempts of human ITx under the standard immunosuppression of that era (steroids, azathioprine, antilymphocyte globulin), but with disheartening outcomes.

Under the era of cyclosporine, the first successful human multivisceral transplantation by Starzl and associates was performed in 1987. Then, in 1988, the transplantation of the first isolated intestinal allograft from a live donor was performed, followed by the first combined liver-intestinal transplantation by Grant and colleagues.

In 1989, with the use of tacrolimus, reports of series of patients undergoing successful ITx were first published. Today, tacrolimus is considered the mainstay of most immunotherapeutic regimens for recipients of ITx.

Indications for Small Bowel Transplantation

Intestinal failure can have life-threatening complications, have high morbidity and poor QOL, or result in early death despite optimal parenteral nutrition (PN). Indications for transplantation due to these consequences are the following:

- Intestinal failure with life-threatening complications:
    - TPN-induced liver disease;
    - recurring catheter related sepsis;
    - impending loss of central venous access; or
    - frequent episodes of severe dehydration despite intravenous fluid in addition to home parenteral nutrition (HPN).
- Intestinal failure with high morbidity and poor QOL:
    - frequent/chronic hospitalisations;
    - narcotic dependency;
    - inability to function (i.e., pseudo-obstruction, high output stoma); or
    - patient's unwillingness to accept long-term HPN.
- Intestinal failure virtually resulting in early death despite optimal PN:
    - extremely short bowel syndrome;
    - congenital intractable mucosal disorder; or
    - desmoid tumours associated with familial adenomatous polyposis.

Contraindications for Small Bowel Transplantation

Contraindications for small bowel transplantation can be absolute or relative. Absolute contraindications include:

- nonresectable malignancy (local or metastatic);

- severe congenital or acquired immunological deficiencies;

- advanced cardiopulmonary disease;

- advanced neurological dysfunction;

- major psychiatric illness;

- sepsis with multisystem organ failure;

- multisystem autoimmune diseases;

- life-threatening and other noncorrectable illnesses not related to the digestive system;

- demonstrated patient noncompliance with medical recommendations; and

- insufficient vascular patency for central venous access for up to 6 months following ITx.

Relative contraindications include:

- history of cancer in the past 5 years;

- physical debilitation;

- lack of family support;

- infants weighing less than 5 kg; and

- multiple previous abdominal surgical procedures.

Donor Selection and Preparation

The selection of a donor for ITx is based on ABO blood type, organ size compatibility, and virus serological results. Human leukocyte antigen (HLA) typing and cytotoxic crossmatch have not been universally adopted to the selection criteria. Preparation of the graft is done by administration of gut decontaminant solution (amphotericin B, polymixin B, gentamycin) through a nasogastric tube and intravenous antibiotics; this should be done as soon as possible.

Candidate Evaluation

A thorough and comprehensive multidisciplinary evaluation of patients with intestinal failure is essential to assess appropriate candidacy for transplantation and provide the best possible outcome for these complex patients. Candidates must be assessed from surgical, medical, and psychosocial perspectives by the transplant team and various consultants.

Living-Donor Intestinal Transplantation

The role of living-donor intestinal transplantation (LDITx) is not as well defined, mostly due to limited experience with the procedure.

The potential advantages of LDITx include the elimination of waiting time; minimisation of cold ischaemia time; better preservation of mucosal integrity; reduction of the risk of systemic sepsis from bacterial translocation; better HLA matching, reducing the risk of acute rejection; an elective surgery setting with shorter hospitalisation stays; and fewer hospital readmissions than reported following cadaveric ITx. The main disadvantage is the operative risk for the donor and the potential problems associated with the use of a shorter graft.

The donor's safety is the most important consideration in LDITx. The operative risk of a healthy adult undergoing elective segmental bowel resection is quite low—surely comparable to the risks taken by a living kidney donor for elective nephrectomy, and inferior to the risk of right hepatectomy for adult-to-adult living-donor liver transplant.

Operative Procedures

The fundamental strategy of multivisceral organ retrieval focuses on isolating the organs that will be procured for each individual recipient, and core cooling them with an infusion of a preservation solution (the University of Wisconsin solution). Multivisceral on-block retrieval, which includes the stomach, duodenum, pancreas, liver, and small intestine, is the parent operation, which bases its blood supply on the celiac and superior mesenteric arteries.

Five general graft options are available for ITx candidates, depending on the integrity of the remnant gastrointestinal tract and the status of the other visceral organs:

- isolated bowel consisting of all or part of the jejunoileum;

- combined liver and intestinal graft;

- multivisceral graft consisting of the liver, stomach, pancreas, duodenum, and jejunoileum;

- modified multivisceral graft to include the previous option without the liver; or

- isolated liver graft.

Isolated intestinal transplant

The basic steps for an isolated intestinal transplant procedure are as follows:
Step 1: Donor operation (organ procurement, cadaveric):

- The aorta and inferior vena cava (IVC) and mesentery root are exposed retroperitoneal.

- The infrarenal aorta is cannulated and systemic heparinisation is carried out.

- The IVC above the diaphragm is sectioned and the thoracic aorta is cross-clamped.

- The visceral organs are perfused with cold preservation solution.

- The entire intestine is mobilised and the duodenum and distal ileum are stapled.

- The superior mesenteric artery (SMA) and superior mesenteric vein (SMV) are dissected and divided.

- The liver, small bowel (SB), pancreas, and spleen are removed en bloc.

Step 2: Back-table preparation and core cooling with an infusion of the preservation solution:

- The liver is separated.

- The SMA is dissected until the first jejunal branch.

- The celiac trunk is dissected and the splenic artery is divided.

- The bile duct is divided at the superior aspect of the head of the pancreas.

- The SMV and portal vein are dissected.

- The neck of the pancreas is divided.

- The splenic vein is ligated and divided.

- The anterior surface of the portal vein and distal end of the bowel are marked.

Step 3: Recipient operation (implantation of the graft with establishment of vascular anastomosis and gastrointestinal tract (GIT) reconstruction) involves the following:

- arterial inflow: SMA versus infrarenal aorta;

- venous outflow: portal (SMV or portal vein) versus systemic (IVC or left renal vein);

- GIT reconstruction: proximal and distal anastomosis with creation of a proximal stoma;

- biliary reconstruction; and

- a double lumen gastrojejunostomy tube.

Combined liver and intestinal transplant

The basic steps for a combined liver and intestinal transplant procedure are as follows:
Step 1: Donor operation (organ procurement):

- The organs are procured en bloc with preservation of the celiac artery and SMA with a Carrel patch of the aorta.

- IVC is divided just above the diaphragm suprahepatic and just above the renal veins infrahepatic.

Step 2: Back-table operation and core cooling with an infusion of the preservation solution:

- The Carrel patch is anastomosed to a conduit of the donor thoracic aorta.

Step 3: Recipient operation (implantation of the graft with establishment of vascular anastomosis and GIT reconstruction) involves the following:

- removing the diseased organs;
- donor aortic conduit anastomosed end-to-side with recipient aorta;
- donor suprahepatic IVC anastomosed to recipient hepatic veins;
- portal vein anastomosis;
- reperfusion; and
- GIT and biliary reconstruction.

Multivisceral transplantation

Multivisceral transplantation has the following features:

- The abdominal exenteration results in a larger cavity for the new graft.

- There are fewer vascular and enteric anastomoses.

- The vascular inflow to the multivisceral graft can be obtained either from the infra- or suprarenal aorta.

- The outflow of the graft is via the suprahepatic vena cava of the donor.

For a living-related donor for intestinal transplantation, the procedure includes:

- A 150–180-cm graft of small bowel is measured, starting 20 cm from the ileocaecal valve (ICV), making sure to leave at least 60% of the small bowel for the donor.

- Arterial inflow is through the terminal branch of the SMA just distal to the take-off of the ileocaecal branch, with its vein next to it.

Postoperative Management

Medical

Immediately postoperative, the patient is transferred to the paediatric intensive care unit (PICU) where meticulous assessment should include respiratory status, oxygenation and ventilation, fluid status, cardiovascular status, renal function, neurological status, electrolyte balance, surgical dressings and drains, any bleeding, pain management, and medication administration. Frequent monitoring of vital signs and obtaining blood for laboratory tests is also done. Doppler US is routinely performed on postoperative day 1 to assess vessel patency or as clinically indicated.

The intermediate phase of care begins approximately 7 or 8 days after transplantation. By this time, most patients have been extubated, have had most monitoring lines removed, and have been stabilised enough to transfer to the paediatric step-down unit. The assessment continues to cover the major organ systems.

Immunosuppression

Over the past decade, new potent immunosuppressives have become available. The introduction of tacrolimus has improved patient and graft survival rates and continues to be the cornerstone of most immunosuppressive regimens after ITx.

Most successful immunosuppressive regimens currently are based on tacrolimus and steroid therapy. Several centres are adding third agents to this cocktail to improve success. Still, rejection, infection, and immunosuppressive-related side effects are common. These issues have driven efforts towards the development of newer, novel immunotherapeutic protocols. The most promising current protocols involve the addition of the interleukin-2 receptor antagonist, sirolimus, rabbit antithymocyte globulin, and alemtuzumab.

Monitoring of the graft function

Monitoring of the graft function is clinically in the first line. Symptoms of graft dysfunction are ballooned abdomen, abdominal pain, liquid diarrhoea, vomiting or ileus, and dark purple color of graft mucosa. Further diagnostic examination contains an endoscopic inspection of the graft with serial biopsies. Endoscopic access is via the grafts ileostomy. During the early postoperative phase, graft endoscopies are performed twice weekly.

A helpful development was the introduction of zoom endoscopy, which allows better macroscopic inspection of the villus. An intestinal contrast media passage is performed at postoperative day 4 or 5 to verify patency of the gastrointestinal anastomoses. At present, specific parameters for monitoring of intestinal graft function are currently not available. Thus, laboratory chemistry is restricted to routine parameters.

Postoperative Complications

Rejection

After sepsis, rejection is the second most common cause of death in small bowel transplant recipients, but it is the primary reason for graft loss. In practice, rejection and infection often occur simultaneously, and it may be difficult to determine which one is the dominant pathologic process.

Higher immunosuppressive maintenance therapy in the intestinal transplanted patient increases the risk of infection, tacrolimus-induced nephrotoxicity, and posttransplant lymphoproliferative disorder (PTLD).

The clinical presentations of acute rejection include fever, diarrhoea, malabsorption, bloody ostomy drainage, paralytic ileus, or an increase in liver function tests. Fever is the most common presentation. Diarrhoea is also a common manifestation of acute rejection. The amount of ostomy output should be monitored closely. A significant decrease in ostomy output, however, can also reflect rejection because bowel motility can be suppressed by rejection, similar to paralytic ileus.

Acute episodes of rejection occur early posttransplant, mostly within the first 6 months, and then decline rapidly with very few episodes observed past 2 years after transplant.

An assessment of acute rejection in ITx is based primarily on pathological findings found on multiple biopsies taken during endoscopic survey. Endoscopy and biopsies should be performed twice weekly during the patient's initial 2-3 weeks posttransplant hospitalisation, then weekly over the next 3 months, and then monthly until stoma closure. During the course of any rejection, biopsies should be performed at least twice a week.

Prevention and treatment of rejection are the most difficult and most important dilemmas in clinical intestinal transplantation. Early detection of rejection and timely initiation of treatment are critically important for intestinal transplant recipients. The recent introduction of daclizumab as a third agent to be administered with corticosteroids and tacrolimus for induction therapy has improved early postoperative outcomes.

Treatments for acute rejection include augmentation with steroids, upward adjustment of the tacrolimus level, or the use of antilymphocyte antibody immunosuppression, such as OKT-3.

Infections

Infection is a significant postoperative complication with any solid organ transplant patient due to the use of immunosuppressive medication to control rejection. As noted earlier, immunosuppression is kept at higher levels within these intestinal transplanted patients to decrease episodes and severity of rejection. This increases the risk of infection. The literature reports that 91% of transplant recipients developed infectious complications within the first year of transplantation.

Posttransplant lymphoproliferative disease

PTLD is the most common cause of late graft loss in ITx. This high incidence of PTLD in ITx recipients is likely related to the high level of immunosuppression in these patients and possibly from the high lymphoid cell content in the intestinal allograft.

The term "EBV-associated PTLD" is used to include all clinical syndromes associated with EBV-driven lymphoproliferation, ranging from a benign self-limited form of polyclonal proliferation to true malignancies containing clonal chromosomal abnormalities. Pathology remains the gold standard for PTLD diagnosis.

In the absence of reliably effective therapy for all stages of PTLD, the optimal strategy for management is currently focused on prevention. Recommended strategies for prevention are identification of the patient at high risk for PTLD development prior to transplant to be adequately monitored. Aggressive immunosuppression should be employed only in the presence of biopsy-proven acute rejectiManagement includes reducing immunosuppression, surgical resection, local irradiation, antiviral agents (acyclovir, ganciclovir), and passive antibody (intravenous immunoglobulin, or IVIG). When reduction in immunosuppression fails, anti-CD20 antibody (e.g., rituximab) represents an attractive second-line therapeutic option because of its low toxicity.

Graft versus host disease

Graft versus host disease (GVHD) occurs when immunocompetent donor lymphoid cells damage recipient tissues after allogeneic transplantation. The major targets are epithelial cells of the skin, intestine, and liver. This complication had been anticipated after clinical intestinal transplantation because the large inoculum of lymphoid cells in a small bowel graft was predicted to increase the likelihood of this disease. The diagnosis of GVHD is based on clinical presentation and includes a skin biopsy for histopathological confirmation.

The development of GVHD is almost always associated with a low level of immunosuppressive agents, and patients usually respond well to the augmented immunosuppression.

Other postoperative complications

Other postoperative complications include recurrence of the original disease and preservation and reperfusion injury.

Surgical Complications

Surgical complications that need emergency operations are graft duodenal stump leaks, spontaneous small bowel perforations, abdominal compartment syndrome, acute bowel obstruction, wound dehiscence, biliary stricture, reflux at esophagogastrostomy, pancreatitis, intraabdominal haemorrhage, intraabdominal abscess, and anastomotic leaks occurring at the coloanal and esophageal anastomosis leading to peritonitis. Graft-associated vascular complications include hepatic artery thrombosis, disruption of the aortic anastomosis, portal vein stenosis, and chylous ascites.

Outcome and Quality of Life

The University of Pittsburgh Medical Center has the largest single experience in transplantation worldwide; the present transplant rate exceeds 60 cases per year. Their latest reported figures showed a 1-year patient survival of 92% in 89 patients transplanted between 2001 and 2003. The numbers of successful intestinal transplants that are now more than 10 years posttransplant are accumulating, with the longest survivor now approaching 15 years posttransplant.

Following transplantation, overall QOL improved significantly; there was an average improvement in all the parameters in patients following transplantation; and significant improvements were seen in psychological, physical, and social aspects.

Survival of intestinal transplant recipients can be expected to improve further with earlier referral, as the procedure is more successful when patients are transplanted from home. Successful outcome should not be judged on survival alone, however. It is reasonable to know whether the quality of the extended life is good, thus justifying the stress of further surgery and hospitalisation.

Evidence-Based Research

Table 126.2 presents a study on health-related quality of life (HRQOL) for liver transplantation children younger than 5 years of age, comparing those with living-related and cadaveric donor liver transplantation (CDLT).

Table 126.2: Evidence-based research.

Title	Impact of liver transplantation on HRQOL in children less than 5 years old
Authors	Cole CR, Bucuvalas JC, Hornung RW, Ryckman FC, et al.
Reference	Pediatric Transplantation 2004; 8:222–227
Problem	Assess health-related quality of life (HRQOL) score in comparison to type of liver transplantation whether cadaveric or living-related.
Intervention	adaveric donor liver transplantation (CDLT), living-related liver transplantation (LRLT)
Comparison/ control (quality of evidence)	HRQOL scores were determined before and one year after transplantation. In addition, demographic and clinical factors associated with QOL were assessed during the period of the study, which was between October 1997 and January 2002.
Outcome/ effect	The baseline infant-toddler health status questionnaire (ITHQ) subscale score was greatest for global mental health (GlobalMH); the score improved significantly during the first 6 months after transplantation, and the score steadily improved over the rest of the first year. The ITHQ subscale score at baseline was similar for children receiving CDLT and those receiving LRLT. Children with biliary atresia had lower baseline scores than those with other diagnoses. Multivariant analysis conducted to identify independent predictors of the ITHQ subscale score revealed that donor type had no effect on QOL parameters.
Historical significance/ comments	This report on assessment of HRQOL in children younger than 5 years of age receiving liver transplantation emphasized that the functional health of children who received LDLT was similar to that of children who received CDLT. Further analysis showed that functional health improves with time elapsed since transplantation in both groups. These results are similar to those obtained in older children (>5 years of age) who underwent liver transplantation. In this study, age at transplant had a negative effect on the impact of the illness on the patient. Age at transplantation did not affect any of the other scales of ITHQ. GlobalMH improved with an increase in the number of inpatient hospital days. The study had several limitations: (1) basing the study on the experience of a single paediatric liver transplant program limited its sample size and statistical power; (2) all demographic characteristics of families are representative of the population referred to that institution for transplantation but may not reflect those at other centres; and (3) the bias of the parents in completing the questionnaire. The authors concluded that HRQOL improves after transplantation in all of their patients irrespective of the donor type. As the number of paediatric patients who receive liver transplantation increases, it is important for health care providers and families to be aware of HRQOL improvements. Functional health, clinical outcome and cost must be part of the discussion between caregivers, health professionals, policy makers, and third-party payers. Assessment of HRQOL should be an integral part of the care of liver transplant patients and their caregivers.

Key Summary Points

1. Paediatric transplantation is considered one of the difficult tasks to be achieved in the African continent due to lack of resources, cadaveric programs, and technical facilities, as well as delayed referral of cases.

2. Liver transplantation is now the standard treatment for end-stage liver disease in children.

3. Extrahepatic biliary atresia is the main indication for paediatric liver transplantation, constituting 60–70% of the indications.

4. Malnutrition, vaccination problems, and long waiting lists are major pretransplant issues still to be addressed.

5. Small-sized vessels, donor-recipient size mismatch, and previous surgeries are all technical difficulties unique to paediatric liver transplantation.

6. Vascular complications, especially hepatic artery thrombosis, are not still considered a major problem.

7. Although biliary complications are frequent in paediatric living-related transplantation, they are not associated with decreased patient survival.

8. In children, morbidity and mortality rates from infections exceed those from rejection after transplant, and immunosuppression can hinder growth, renal function, and graft tolerance.

9. Intestinal transplantation is a more advanced procedure, with mainly cadaveric donors.

10. Liver and intestine or en bloc transplantation has better results than intestinal alone.

11. Both infection and rejection contribute to the lower success rate of combined liver and intestine or en bloc transplantation compared to liver transplantation.

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